State of the Art in Malignant Melanoma Therapy: Bench to Bedside

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Disclosures
Ad Boards: OncoSec, NeoStem, Nektar, Prothena

The presentation will discuss but not endorse the use of investigational agents and the possible use of drugs for as yet unapproved indications.

Topics to cover—immuno

Bench
- Interferons
- Interleukin-2
- CTLA4 blockade
- PD-1, PD-L1 blockade
- Tumor-infiltrating lymphocyte regimens
- Lesional, local approaches

Bedside
- Adjuvant>>advanced
- Proof of principal but poor therapeutic index
- Checkpoint blockers augment existing immune response
- TIL cells exploit immune tumor microenvironment
- Potent locoregional responses → systemic benefit

Topics to cover—molecular

Bench
- Discovery of BRAF activating mutation in melanoma
- Other oncogenic drivers, some in other tumors
- Rapid emergence of resistance uncovered multiple new targets
- Combinations appear promising therapeutically

Bedside
- Rapid and dramatic responses to specific BRAF inhibitors
- Equally dramatic emergence of resistance, sometimes mixed
- Therapeutic index and drug interactions may limit combinations (like early ART)

Interferons—type I and II

Bench
- IFN-α has pleiotropic immunomodulatory effects
- Modest activity vs advanced melanoma but optimal with tumor burden
- Poorly “customized” re: predictors of benefit/failure/toxicity
- IFN-γ—narrower, different immunomodulatory effects but hard to harness therapeutically

Bedside
- Widespread use in adjuvant Rx at high doses/long durations
- Controversy remains re: risk and cost/benefit ratios
- IFNs likely to be supplanted by narrower activity cytokines in cancer

Interleukin-2

Bench
- Murine data showed benefit dependent on dose, elaboration of LAK cells
- Receptors related to other yc cytokines
- Toxicities mediated by capillary leak, other cytokines
- Mechanisms poorly understood: increased AICD, Treg undesirable

Bedside
- High doses required for clinical benefit=5-7% durable remission
- Multi-organ toxicities life-threatening, limit access to selected pts, Rx centers
- Predictive factors may be based on host, tumor factors (CWG “select”)
- Altered versions, enhancements and toxicity protectors all failed
- Lower doses → T cell survival in adoptive T cell Rx
**CTLA4 blockade**

**Bench**
- CTLA4 competitively inhibits CD28:B7.1 binding after T cell activation
- Embryonic -/- causes lethal lymphoproliferative syndrome
- Ab to CTLA4
- Removes the inhibitory signal
- Depletes Treg cells
- Enhances melanoma-specific T cell motility

**Bedside**
- Fully-human CTLA4 Ab active in melanoma, sometimes with delayed response
- Autoimmunity in up to 30%
- Colon, Skin
- Pituitary
- Liver
- Others rarely
- Approved for advanced melanoma, RFS benefit in adjuvant melanoma

**PD-1 axis blockade**

**Bench**
- PD-1 mediates T cell exhaustion in viral, tumor immune responses
- Ligands—PD-L1, PD-L2
- PD-1 -/- phenotype
- Blockade on either side reverses exhaustion

**Bedside**
- Phase I studies showed early, marked regression in 30-40% of patients
- Several human or humanized Abs studied, 2 approved 2014
- Nivolumab in Japan
- Pembrolizumab in U.S. (accelerated, 2nd/3rd line)
- Plls test benefit of PD-1 and/or combined PD-1/CTLA4 block
- Will PD-1 or PD-L1 block or combination with ipi "win"?

**Other immunotherapy combinations**

**Bench (or early trials)**
- Inhibitors of negative regulators in tumor microenvironment
  - IDO inhibitor of MDSC
  - PLX3397 inhibitor of RTKs in tumor macrophages
- Immune costimulation
  - 4-1BB-Ab, CD40L, OX40-Ab
  - GM-CSF with ipilimumab
- Vaccines?

**Bedside (later trials)**
- CTLA4 +/- bevacizumab
- Other yc cytokines, e.g. IL15 + PD-1 blk
- CTLA-4 Ab plus radiotherapy
- Enhancers of ADCC
- Lesional, regional delivery
- Viral imm'mod genes
- Cytokines, DC activators

**Tumor-infiltrating Lymphocytes**

**Bench**
- Adaptive/autologous immune cell Rx melanoma—other tumors
- Lymphodepletion required
- T cell expansion and survival are critical
- Exploration of antigen level individual tumor mutations
- Role of tumor manipulations
- Systemic Rxs inc targeted
- Radiotherapy to tumor
- "Other predictors "necessary and sufficient" for curative outcomes

**Bedside**
- Requirements daunting
- Tumor accessible
- Yield of TIL culture
- ?tumor-specificity
- Pt who can tolerate lymphodepletion, HDIL-2
- Outcomes encouraging in pts who get all components
- ORR in 60-70% range
- CRR in 15-20% range
- PFS plateau?

**Molecularly-targeted Rx**

**Bench**
- BRAF activating mutations in >50% melanoma
  - Single site in 80%
  - Ras-indepedent activation
  - Transforming
- N-Ras mutations (several sites) in 15-20%, nearly always exclusive of BRAF mut
- Other drivers include CDK, NFI, c-kit, GNA, fusion genes

**Bedside**
- First generation of inhibitors "dirty"
- "occasional response" in unselected pts
- Early trials in unselected pts failed to improve cytotoxic Rx
- Braf assays came with selective BRAF inhibitors
- Dramatic responses if mut+
- Rapid emergence of resistance

**Resistance to targeted Rx**

**Bench**
- Vertical (add MEK inhibitor) and horizontal (inhibit AKT/PI3K path) promising
- Rapid discovery of multiple resistance mechanisms, new drug targets, heterogeneity
  - CDK 4/6
  - Met
- Metabolic shifts, feedback loops and altered addictions

**Bedside**
- MEK inhibitors highly active as single agents in BRAF, not NRAS mutant
- Combined BRAF+MEK inhibition adds benefit
- Horizontal blockade strategies under investigation
- Therapeutic index likely to become unfavorable
**Combination immuno+targeted**

**Bench**
- BRAF inhibition enhances immune functions to control melanoma
- T cell activity
- MHC expression
- PD-1

**Bedside**
- Ipilimumab plus vemurafenib caused hepatotoxicity
- PD-1 blockade plus targeted agents may be more tolerable
- MEK inhibition inhibits T cells—the drugs are not mutation/activation-specific because MEK is upstream-activated

**Pembrolizumab single agent data in advanced melanoma (Ribas et al ASCO 2014)**

**Survival for adv melanoma on nivolumab**

**Vemurafenib + cobimetinib**

(Ribas et al Lancet O, 2014)

**Survival of melanoma pts with brain mets Rx’d with ipilimumab**

Heller ASCO 2011 after Margolin Lancet O 2011

Nivolumab single-agent f/u
Topalian et al JCO 2014
The world is moving fast!

Melanoma